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PATENT SPECIFICATION

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(54) COATING SOLID DOSAGE FORMS

(71) We, SHIN-ETSU CHEMICAL COMPANY LIMITED, a Japanese Company, of 6-1, Otemachi 2-chome, Chiyoda-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to a novel method for coating solid dosage forms with an aqueous liquid containing a film-forming polymeric substance. More particularly, the invention relates to a method for coating solid dosage forms in two steps using two aqueous liquids of a cellulose ether having different concentrations.

In general, solid dosage forms such as tablets, pills, granules and capsules are coated with a coating solution containing a polymeric substance mixed with a suitable organic solvent, optionally with added plasticizers, coloring agents and other additives, in order to give them better mechanical strengths and a pleasant appearance, protect active ingredients contained therein from being affected by the ambient atmosphere, and mask any unpleasant odors and tastes.

The above coating method is much disadvantaged by the essential use of large amounts of organic solvents in the making of the coating solutions, which involves the possibilities of hazardous fire or explosion during coating operations as well as the problems of pollution of the air and working environment due to the purged vapor of solvents when a commercially usual coating apparatus is employed.

Attempts were made to remove the above

disadvantages by condensing the purged vapor of solvents by cooling before it went into the air, but this was found almost impractical since it was difficult to attain the condensation point of the solvent vapor by a simple cooling operation. Other attempts were made also to collect the purged solvent vapor with the aid of adsorbents, such as active charcoal, but this was unsatisfactory since the use of adsorbents was very costly and the results were not always effective.

It was then a natural consequence that the above described problem of air pollution might be avoided if the organic solvent was replaced with water. However, the experiences and tests hitherto on the use of water in place of organic solvents have shown that this involves several adverse effects, rendering the substitution of water impractical. According to the past results, for example, solid dosage forms thus coated become stuck to each other, while many active ingredients contained therein are liable to decompose when contacted with water, resulting in a tendency to the collapse of the dosage forms. Further the rate of evaporation of water is generally very low, compared to that of most organic solvents and, as a result, much longer is required for the coating process, leading to a lower productivity and, accordingly, higher coating costs.

Additionally, it is usual to manufacture sugar-coated tablets by providing a waterproof layer of undercoating on the surface of each untreated tablet unit to protect the drug from possible disintegration due to the subsequent sugar coating which is used in the form of an aqueous solution. As such water-

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proof undercoating is used an ethalolic solution of, for example, shellac. The use of the ethanolic solution of shellac for the undercoating presents problems of, on one hand, air pollution as discussed above and, on the other hand, the lower availability of active ingredients of the tablets in the stomach or intestines due to the impermeability of the shellac layer against the digestive fluids.

It is an object of this invention to provide a method of coating solid pharmaceutical dosage forms with an aqueous liquid that does not impair the integrity of the dosage forms and active ingredients contained therein. It is another object of the invention to provide such a method which is free of the problems of pollution of the air and working environment to be caused during the coating operations.

In accordance with this invention, solid dosage forms are coated with an aqueous coating liquid containing a film-forming polymeric substance dissolved or dispersed therein and having a viscosity of at least 3 centipoise as measured at the temperature of coating.

The inventors of this invention have prepared a variety of solid dosage forms that could easily swell and decompose on contact with water and observed how they behave when put into aqueous solutions and dispersions of various polymeric substances as well as in water. As the result, it has been discovered that the lengths of time for these dosage forms to begin swelling and decomposing on contact with any of the aqueous liquids do not depend on the kinds of the polymeric substances or their concentration in the liquids, but depend merely on the viscosities of the liquids, the higher the viscosities, the longer the time required till swelling takes place. In other words, it has been made clear by the inventors that as the viscosity of an aqueous solution or dispersion of a polymeric substance increases, solid dosage forms become less affected thereby.

The inventors further observed how the same dosage forms as above were affected by application of aqueous solutions and dispersions of various film-forming polymeric substances by means of sprayers and other types of coating apparatus. As the result, it has been found that when the coating solutions or dispersions have a viscosity exceeding 3 centipoise, preferably 10 centipoise, there is no adverse effect on the coatings. In other words, the coating liquids having a viscosity of at least 3 centipoise are capable of producing a satisfactory coatings on solid dosage forms having the most sensitivity to water without the least swelling or disintegration of the dosage forms and their ingredients. The viscosity of the coating liquids as referred to herein is a viscosity measured at the temperature of the atmosphere within the coating apparatus, at which temperature the dosage forms are being coated.

The polymeric substances useful in the coating liquids may be any of those which can be dissolved or dispersed in water and have a film-forming property. Examples from the practical point of view are as follows. Water-soluble cellulose ethers, such as methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose and sodium carboxymethylcellulose; water-soluble vinyl polymers containing units of vinyl alcohol, vinyl pyrrolidone, sodium acrylate, acrylic acid or acrylic ester and copolymers thereof; natural polymers, such as gelatin, gum arabic and sodium alginic; aqueous emulsions of polymeric substances prepared by the emulsion polymerization of polymerizable olefinic monomers, such as vinyl acetate, acrylic acid, acrylic esters, methacrylic acid, methacrylic esters, ethylene, esters and anhydride of maleic acid; and the mixtures thereof.

Any of the above-mentioned film-forming polymeric substances can be used to prepare the coating liquids in the form of an aqueous solution or dispersion, having a viscosity of 3 centipoise or more so that no swelling and decomposing phenomena take place on the part of the coated dosage forms. There is, however, a general weak point in the use of water as the solvent for the preparation of the coating liquids, in that since water itself evaporates much more slowly than an organic solvent, which has been used in the making up of the conventional coating solutions, the coating time is accordingly prolonged and, on the other hand, the solid dosage unit forms being coated tend to stick to each other, resulting in irregular thicknesses of coatings. If this is taken into consideration from the commercial and economical standpoints, the preferred film-forming polymeric substances may be, among other examples, water-soluble cellulose ethers, which have a viscosity in the range of from 1.5 to 80, preferably 1.5 to 20, centipoise at 20°C in a 2% aqueous solution.

It may be added in this connection that an aqueous solution of a water-soluble cellulose ether used in the form of aqueous coating solutions is found to make solid dosage forms less sticky to each other during the coating operations than the other water-soluble vinyl polymers or copolymers and natural polymers, though the reasons therefor are not clear. Further, with respect to the above-mentioned viscosity of the water-soluble cellulose ether in a 2% aqueous solution, it is known that when it is less than about 1.5 centipoise, the resulting coatings on solid dosage forms will be brittle and unsatisfactory for the purpose, while, when it is more than about 80 centipoise, the coating solutions will have to be greatly diluted with water to obtain smooth coatings on solid dosage forms, and the use of such dilute solutions results in economic disadvantages, for example, the prolongation of

coating time and the need of much heat for evaporation of the diluting water.

The concentration of the cellulose ethers in the aqueous coating solution is preferably in the range of from 5 to 25% by weight. Lower concentrations than 5% gives rise to the disadvantage of much longer time necessary for attaining desired thickness of the coating. On the other hand, higher concentrations than 25% meet with the difficulty that the surface of the coated solid dosage forms becomes remarkably rugged and the thicknesses of the coatings are irregular due to coarsened spray droplets obtained from the coating solution of the higher concentrations.

In order, therefore, to obtain pretty looking coatings on the solid dosage forms in a preferred embodiment by using the coating solution or dispersion of a cellulose ether or other film-forming polymeric substances in water, it is proposed to carry out the coating in two steps which consist of a first step in which is used the coating solution or dispersion containing the polymeric substance in a high concentration, say in the range of 5% to 25% by weight, and a second step in which is used a smaller amount of the coating solution or dispersion containing the polymeric substance in a lower concentration, say in the range of 0.5% to 10%. In the embodiments, the polymeric substance or cellulose ether in particular is preferred to have a viscosity in the range of 1.5 to 20 centipoise measured at 20°C in a 2% aqueous solution for the purpose of reducing the stickiness between individual dosage unit forms being coated, and a viscosity in the

range of 1.5 to 80 centipoise as similarly measured for the purpose of increasing the gloss of coated dosage unit forms. The gloss of the coated dosage forms is improved by the second step coating in a short time. The polymeric substance used in the second step may be different from that used in the first step so long as its viscosity is within the specified range.

With respect to the concentration of the cellulose ether in the coating liquid used in the second step, it has been established empirically that it should preferably be below 5% by weight but above about 0.5% by weight so that the finished dosage forms may have sufficiently glossy surfaces in a short time.

The fundamental concept of the two-step coating in accordance with the present invention is such that the first step coating is conducted with an aqueous solution of a cellulose ether having a concentration as high as possible in order to achieve the desired thickness of coatings within a short time, regardless of the gloss of the coated products and the second step utilizes an aqueous solution of the same or different cellulose ether having a relatively low concentration as the finish for glossy surfaces, with the highest efficiency of the overall coating process.

To further explain the relations existing between the first and second coating solutions of the cellulose ethers with respect to their concentrations, the following table shows a rough standard recommended depending on the viscosity or polymerization degree of each cellulose ether.

Viscosity in a 2% solution at 20°C, centipoise	Concentration in the first step coating solution, % by weight	Concentration in the second step coating solution, % by weight
1.5—5	10—25	below 10
5—10	7—15	below 7
10—20	5—10	below 5
20—80	—	below 4

The above table is understood also to show the combinations of cellulose ethers in the case where the cellulose ether used in the first step coating is different in kind and viscosity from the cellulose ether used in the second step coating. For example, when the cellulose ether used in the first step coating is of a viscosity of 20 centipoise and that used in the second step is of a viscosity of 1.5 centipoise, the concentrations applicable in the first and second step coating will be in the ranges of 5—10%, e.g. 5% and below 10%, e.g. 9%, respectively.

The first step coating is primarily intended to give the necessary thickness of coatings in a

short time, using a solution of the polymeric substance of a high concentration, regardless of the gloss of the coated surfaces, while the second step coating is intended to provide highly glossy finishes, using a solution of the polymeric substance of a low concentration.

The mechanism by which the highly glossy coated dosage forms are obtained in a short time in the two-step coating process has not been elucidated. Presumably the lower the viscosity of the coating solution is and the lower the concentration of the coating material in the coating solution is, then the easier will be the spreading of the coating solution on the

surface of the solid dosage forms to be coated and smoothness of the coating films, resulting in the production of glossy surfaces. On the contrary, a higher viscosity of the coating solution and a higher concentration of the coating material in the coating solution result in the insufficient spreading of the solution when the solution is brought into contact with the surfaces of the solid dosage forms to be coated, and the coating solution becomes dry to produce dried films lacking in smoothness and gloss on the surface.

In the coating process with an aqueous coating solution of film-forming polymeric substances in accordance with the present invention, it is optional to admix the coating solution with various auxiliary additives employed in the prior art method, including coloring agents, such as edible dyes, edible lake pigments and inorganic pigments, e.g. titanium dioxide, body pigments, such as talc and finely divided silica, plasticizers, such as polyethyleneglycol, polypropyleneglycol and glycerin, flavorings such as vanilla essence and orange oil, and sweeteners such as sugar and saccharine.

Those additives which are used in the coating solution for the first step coating may optionally be added to the coating solution for the second step coating. Incidentally, pigments as the coloring agent are added preferably in the coating solution for the first step, but not in the coating solution for the second step since it is difficult to produce sufficient gloss by a coating solution containing pigments.

With respect to the apparatus employed for coating of the solid dosage forms in accordance with the present invention, using an aqueous solution of a cellulose ether with or without the addition of additives, there are no specific limitations and any of the conventional coater machines can be employed. They include pan coaters of the conventional type, rotating-drum type coaters, such as Accelacota made by Manesty Co., England, Wurster type fluidizing coater developed by the Foundation of Wisconsin University, U.S.A. and the fluidizing coater made by Glatt Co., West Germany. The conditions for operating these coating machines for carrying out the method of the present invention are the same in principle. As heretofore, the only thing that is different being the coating solution in which water is used in lieu of organic solvents. Due to the absence of organic solvent in the coating solutions fed to the coating machines, the danger of hazardous fire and explosion and the problem of air pollution by the purged vapor of the solvents as well as the health problem of workers by the environmental pollution can completely be eliminated.

The thicknesses of coatings provided on solid dosage forms are, of course, variable depending on factors, such as, the kind of the polymeric substance used, the shape and dimen-

sions of the solid dosage forms and the active ingredients contained therein. In most cases, the coatings have a thickness in the range of from 0.005 to 0.5 mm, which, however, does not limit the scope of the invention.

Further respecting the thickness of the coatings produced by the two-step process, it is usual that the second coating has a considerably smaller thickness than the first coating, the thickness of from 0.002 to 0.02 mm being often sufficient for the second coating depending on the desired gloss of the coated surfaces.

The following examples illustrate the present invention. Parts in the examples are all parts by weight, unless otherwise mentioned.

Example 1.

A mixture of 24 parts of lactose and 16 parts of corn starch was kneaded with a 15% ethanolic solution of 0.6 part of polyvinylpyrrolidone (K-30). The resulting mixture was subjected to granulation by an extrusion granulator through a screen having 0.6 mm openings, and the granules thus produced were dried in an oven of the air-circulation type at 50°C for 6 hours. The dried granules were blended with 50 parts of microcrystalline cellulose ('Avicel', product of Asahi Chemical Industry Co., Ltd., Japan—'Avicel' is a Trade Mark), 10 parts of calcium carboxymethylcellulose (tradename: ECG-505, product of Daicel Co., Ltd., Japan) and 0.5 part of magnesium stearate. The resulting product was treated by a rotary tablet machine to form tablets, each 9 mm in diameter and 280 mg in weight.

The tablets were found to have a hardness of 9 kg as determined by a Monsanto Hardness Tester and disintegrate within a period of from 9 to 11 seconds when tested by the disintegration test for "uncoated tablets" in accordance with the U.S. Pharmacopeia, 18th Revision.

The tablets were treated with a drop of water put on their surfaces, to find that the areas in contact with water became swelled and deformed in 0.2 to 0.3 of a second, and the deformed portions were disintegrated after a few minutes.

The tablets were tested also for the disintegrability in contact with the various aqueous liquids (solutions or dispersions) of film-forming polymeric substances or sugar, as mentioned in Table I, accompanied by their respective solid contents, viscosities and the temperatures at which the tests were carried out, by placing 0.02 ml of each liquid onto the convex area of the tablet surface and determining the time before swelling began taking place. Such time will be termed "swelling time" hereinafter. The test results are set out in the same table. These results indicate that the swelling time depends definitely upon the viscosity of the testing liquid at each temperature, irrespective of the kind of the film-form-

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ing polymeric substance and the concentration of the testing liquid. It is found that the swelling time increases with the viscosity of the testing liquids almost linearly in a logarithmic plotting.

On the other hand, the swelling time for the testing liquids containing a low molecular weight substance such as sugar deviates widely from the relationship between the swelling time and the viscosity of the testing liquids.

obtained for the testing liquids containing film-forming polymeric substances. Furthermore, powders of a water-insoluble inorganic substance, such as talc, admixed with the testing liquids do not influence the relationship between the swelling time and the viscosity of the liquids, though such additions remarkably increase the apparent viscosity of the testing liquids.

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TABLE I.

Sample No.	Testing Liquid	C	V	T	S
1	Water	—	0.6	20	0.2
2		—	1.0	40	0.3
3		0.5	1.3	40	0.4
4		1	2.5	40	0.5
5	Aqueous solution of hydroxypropyl-	2	6.1	20	1.4
6	methylcellulose (Viscosity in a 2% aqueous	3	11.2	30	1.8
7	solution at 20°C: 6.1 cps)	5	30.5	20	4.5
8		5	23	40	3.7
9		10	339	20	32
10		10	189	40	21
11	Aqueous solution of hydroxy-	1	3.4	40	0.7
12	propylmethylcellulose	3	35.3	20	5.6
13	(Viscosity in a 2% aqueous	3	30.8	30	5.2
14	solution at 20°C: 15.3 cps)	5	94.6	40	9.5
15	Aqueous solution of hydroxy-	0.5	3.6	40	0.8
16	propylmethylcellulose	1	4.2	20	0.9
17	(Viscosity in a 2% aqueous	2	42.6	30	5.2
18	solution at 20°C: 51.5 cps)	5	368	40	43
19	Aqueous solution of hydroxy-	2	6.9	40	1.5
20	propylcellulose	3	16.0	30	2.7
21	(Viscosity in a 2% aqueous	3	13.8	40	2.2
22	solution at 20°C: 8.2 cps)	5	56.1	20	8.6
23		10	327	40	26
24		2	2.8	20	0.7
25	Aqueous solution of vinyl	5	5.2	40	0.9
26	pyrrolidone (K-30)	10	7.4	30	1.2
27		20	16	40	3.2
28		3	2.8	40	0.6
29	Aqueous emulsion of polyvinyl acetate	5	4.3	20	0.7
30		10	16	30	2.3
31		30	4.6	40	2.2
32	Aqueous solution of sugar	40	6.7	40	6.4
33		50	10.5	40	29
34	Sample 9 added with 10% of talc	15	640	20	32
35	Sample 21 added with 10% of talc	13	27.2	40	2.2

Notes: C is for concentration in a % by weight
 V is for viscosity of liquid in centipoise.
 T is for temperature at which the test was undertaken.
 S is for swelling time in seconds.

Next, the tablets were subjected to coating tests by spraying the aqueous coating liquids prepared by dissolving or dispersing various kinds of film-forming polymeric substances in water. Spraying of pure water was also conducted in parallel in the same coater machines in investigate the effects of water on the tablets.

The coating machines employed for the tests were a conventional pan coater with a pan of 40 cm in diameter, a Glatt fluidizing coater of Model WSLD-3 and a Wurster fluidizing coater having a column of 14 inches in diameter. The manner and conditions for operating each coating machine were as follows.

As to the pan coater, 3 kg of the tablets were charged into the pan. Spraying of the coating liquid and blowing of hot air were repeated 3 times alternately, the spraying of the liquid lasting for 10 seconds at a time with 3 ml of the liquid at 40°C and the blowing of hot air at 60°C lasting for 30 seconds at a time.

In the Glatt fluidizing coater and the Wurster fluidizing coater, the rates of spraying were 30 ml and 5 ml, respectively, of the coating liquid at 40°C per minute and the tem-

perature of the air for effecting fluidization was also 40°C.

The results of the above coating tests are summarized in Table II. It is clear from the table that the tablets coated with the coating liquids having a viscosity below 3 centipoise became swollen and finally disintegrated while no such adverse effects were brought about by the coating liquids having a viscosity higher than 3 centipoise. The viscosity of 3 centipoise of the aqueous coating liquids corresponds to the swelling time of 0.5 to 0.9 of a second in the relationship between the swelling time and the viscosity of the contacting liquids.

From the results of the foregoing tests, it may be concluded that 0.5 to 0.9 second is sufficiently long for the formation of coating films on the surface of the tablets when the coating liquids are brought into contact with the surface of the tablets without affecting the integrity of the tablets. Swelling of the tablets is caused by the penetration of water into the interior of the tablets. Therefore, no swelling of the tablets suggests the absence of any undesirable effects by water to the active ingredients contained in the solid dosage forms.

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TABLE II.

Sample No.	Testing Liquid	Condition of tablets coated by coater:				
		C	V	X	Y	Z
1	Water	—	0.6	*	**	**
2		0.5	1.3	*	—	—
3	Aqueous solution of H.P.M.C.	1	2.5	*	**	—
4		2	5.6	Good	Good	Good
5	(Viscosity: 6.1 cps)	3	9.5	Good	—	—
6		5	23	—	Good	—
7		10	189	Good	—	Good
8	Aqueous solution of H.P.M.C.	0.5	2.3	*	**	—
9		1	3.5	Good	Good	Good
10	(Viscosity: 51.5 cps)	2	8.5	Good	—	—
11		3	20.8	Good	Good	Good
12	Aqueous solution of H.P.M.C.	0.5	1.6	*	**	—
13		1	2.9	*	—	**
14	(Viscosity: 8.2 cps)	2	6.9	Good	Good	—
15		3	13.8	Good	—	Good
16	Aqueous emulsion of polyvinyl acetate	3	2.8	*	**	—
17		5	3.6	Good	Good	Good
18		10	5.6	Good	Good	—
19	Aqueous solution of Vinyl pyrrolidone	2	1.9	*	**	—
20		10	15.3	Good	Good	—
21	Aqueous solution of sugar	50	10.5	Not disintegrated	—	—

Notes: C is for concentration in % by weight.

V is for viscosity of liquid at 40°C in centipoise.

X is for a conventional pan coater.

Y is for Glatt fluidizing coater of Model WSLD-3.

Z is for a Wurster fluidizing coater having a column of 14 in. in diameter.

"Good" means that coatings as thick as 0.03 mm were obtained without disintegration and decomposition of the tablets.

* indicates that from 2 to 100% of the tablets were disintegrated in 5 minutes after the coating was commenced.

** indicates that from 2 to 100% of the tablets were disintegrated in 10 minutes after the coating was commenced.

H.P.M.C is for hydroxypropylmethylcellulose, the viscosity of which is in a 2% aqueous solution at 20°C.

Example 2.

Coating tests were undertaken on medical tablets containing vitamin B₁ and vitamin C in complex as the active ingredients. The tablets had been prepared as follows.

A well-blended mixture of 5 parts of vitamin B₁, 50 parts of vitamin C and 190 parts of lactose was kneaded with a 15% ethanolic solution of 4 parts of polyvinylpyrrolidone (K-30) and granulated by an extrusion pelletizer having a screen with 0.6 mm openings. The products were dried in an oven of the air-circulation type at 50°C for 6 hours, and further blended with 1 part of magnesium

stearate and processed by use of a rotary tablet machine into tablets of 9 mm in diameter, weighing 250 mg each on an average.

The aqueous coating solution was prepared by dissolving into 90 parts of water 10 parts of hydroxypropylmethylcellulose ("Pharmacoat" 606, product by Shin Etsu Chemical Co., Ltd., Japan—"Pharmacoat" is a Trade Mark) with the contents of hydropropoxy and methoxy groups of 8.9 and 28.7% by weight, respectively, and having a viscosity of 6.1 centipoise at 20°C in a 2% aqueous solution.

As a control solution, another aqueous solution was prepared by dissolving 44.2 parts of

sucrose, 3.3 parts of gelatin and 8.3 parts of gum arabic into 44.2 parts of water.

The tablets were coated with either one of the above two coating solutions, using one of the same coating machines as used in Example 1.

The operation conditions in each of the coating machines were as follows. With the pan coater when hydroxypropylmethylcellulose was employed as the coating material, 3 kg of the tablets were charged into the pan and spraying of the coating solution by use of a spray gun with compressed air and blowing of hot air for drying were alternately performed. The duration of a single spraying was 10 seconds each and the amount of the sprayed coating solution in a single spraying was 3 ml each, while maintaining the temperature of the solution at 40°C. The duration of a single hot-air blowing was 30 seconds each and the temperature of the air was 40°C. When sucrose was employed as the coating material, 1.5 kg of the tablets were charged in the pan and spraying of the coating solution by use of a spray gun with compressed air and blowing of hot air for drying were alternately performed. The duration of a single spraying was 10 seconds and the amount of the sprayed coating solution in a single spraying was 10 ml each while maintaining the temperature of the solution at 40°C. The duration of a single hot-air blowing was 60 seconds each and the temperature of the air was 50°C.

With the Glatt fluidizing coater, 3 kg of

the tablets were charged into the machine and the spraying of the coating solution was carried out at a rate of 30 ml/minute, while keeping the temperatures of the coating solution and the air for fluidization both at 40°C.

With the Wurster fluidizing coater, the quantity of the tablets charged into the machine in one time was 1.3 kg and the rate of spraying of the coating solution was 5 ml/minute. The temperatures of the coating solution and the air for fluidization were both 40°C.

The coating operation with the coating solution of hydroxypropylmethylcellulose was continued until the thickness of the coating layer reached 0.05 mm, while the coating operation with the sucrose-based coating solution was continued until the amount of coating reached 50 mg per tablet. After completion of the coating operation, the coating tablets were dried in an oven of the air-circulation type at 60°C for 5 hours.

Samples of the tablets were collected on 3 occasions, i.e., before coating, immediately after the completion of coating and drying, and after 30 days of storage at 50°C in a glass bottle with a screw-mounted cap. Each sample was analyzed to find its contents of the vitamins, i.e., by the thiochrome method for vitamin B₁ and by the indophenol titration method for vitamin C in order to determine the influence of the coating and storing on the vitamin contents. The results are shown in Table III below.

TABLE III.

Active ingredient	Coating machine	Hydroxypropylmethylcellulose		Sucrose
		Pan coater	Glatt fluidizing coater	Pan coater
Before coating	Vitamin B ₁ , mg/tab.		4.97	
	Vitamin C, mg/tab.		50.6	
After coating and drying	Vitamin B ₁ , mg/tab.	4.95	4.97	4.63
	Vitamin C, mg/tab.	50.3	50.4	46.2
After storage	Vitamin B ₁ , mg/tab.	4.94	4.95	4.25
	Vitamin C, mg/tab.	50.3	50.3	42.8

As is seen from the table, the contents of both vitamin B₁ and vitamin C in the tablets with hydroxypropylmethylcellulose-based coating showed very slight decrease during the coating process and the storage, while remarkable decrease was recorded in the contents of vitamins in the tablets with sucrose-based coating.

Example 3.
This example is given to demonstrate the two-step coating process.

Tablets weighing 300 mg each were prepared by shaping a mixture of 90 parts of aspirin granules and 10 parts of corn starch into tablets with a rotary tablet machine.

The coating solution for the first step coating was prepared by dissolving or dispersing 15 parts of hydroxypropylmethylcellulose (Pharmacoat 603, product by Sin-Etsu Chemical Co., Ltd., Japan) with the contents of hydroxypropoxy and methoxy groups of 9.8% and 29.2% by weight, respectively, and with the viscosity of 3.1 centipoise in a 2% aqueous solution at 20°C, 0.3 parts of titanium dioxide and 0.15 part of tartrazine aluminum lake into 85 parts of water.

The coating solution for the second step coating was prepared by dissolving 4 parts of the same hydroxypropylmethylcellulose as in the first step coating solution in 96 parts of water. As a control, a third solution was prepared by dissolving or dispersing 4 parts of the same hydroxypropylmethylcellulose as in the first step coating solution, 0.08 part of titanium dioxide and 0.04 part of tartrazine aluminum lake in 96 parts of water.

Into an automatic pan coater (Freund Industry Co., Type FM-2) were charged the tablets weighing 2 kg, and the tablets were coated in two ways, namely in either the two-step coating with the coating solutions prepared as above or the single-step coating with the coating solution for control. The alternate spraying for 10 seconds with 1.7 ml of the coating solution and the air blowing for drying for 20 seconds were repeated until the desired thickness of the coating was attained. The temperatures of the coating solution and the air for drying were 40°C and 60°C, respectively.

The first and second step of coating lasted for 110 and 30 minutes, respectively. The weight increase of the tablets by the first step and overall weight increase of the tablets by the two steps were 8 and 8.6 mg per tablet, respectively, and the thickness of the coating layer by the first step and the overall thickness of the coating layer after the finishing were 0.05 and 0.053 mm, respectively.

The control test carried out in a single step with the control solution took about 450 minutes, giving the amount of coating of 8.6 mg per tablet and the thickness of the coating layer of 0.053 mm.

It was observed that the surface of the tab-

lets after the first step coating was found quite mat, while that after the second step coating very glossy. The degree of gloss obtained in the control test was somewhat inferior, despite the much longer duration of the coating operation required.

Example 4.

The coating tests were carried out with aqueous coating solutions in two ways, i.e., the two-step coating and the single-step coating with a control solution.

For the purpose of the two-step coating process, the coating solution for the first step was prepared by dissolving or dispersing 8 parts of methylcellulose ("Methulose", product by Shin-Etsu Chemical Co., Ltd., Japan— "Methulose" is a Trade Mark) with a methoxy content of 28.8% by weight and with a viscosity of 16.1 centipoise in a 2% aqueous solution at 20°C and 0.2 part of tartrazine aluminum lake in 92 parts of water. The coating solution for the second step finishing coating was prepared by dissolving 3 parts of the same methylcellulose as in the first step coating solution in 97 parts of water. The control solution was prepared by dissolving or dispersing 3 parts of the same methylcellulose as in the first step coating solution and 0.045 part of tartrazine aluminum lake in 97 parts of water.

Into a Wurster type fluidizing coater having the column of 4 inches in diameter were charged 1.5 kg of the aspirin tablets prepared in the same manner as in the preceding example and the test runs were carried out. The temperatures of the coating solution and the air for fluidization were 40°C and 60°C, respectively, and the rate of the spraying of the coating solution was 7 ml/minute.

In the two step process according to the present invention, the first and the second step operations lasted for 78 and 20 minutes, respectively. The weight increase after the first step coating and the overall weight increase after completion of the two-step coating of the tablets were 8 and 8.8 mg per tablet, respectively; while the thickness of the coating layer after the first step coating and the overall thickness of the coating layer after completion of the two-step coating were 0.05 and 0.055 mm, respectively. The surface of the thus finished tablets was found smooth and highly glossy.

In the test employing the control solution, the time taken for the operation was 230 minutes, giving 8.8 mg weight increase per tablet on an average and 0.055 mm of the thickness of the coating layer with somewhat inferior gloss on the surface.

Example 5.

This example was to demonstrate the two-step coating process of solid dosage forms, using different coating materials in each step,

i.e., an emulsion-type coating liquid having a high solids content as the first coating and a solution of a water-soluble cellulose ether having a low solids content as the second coating.

5 The pharmaceutical tablets to be coated were prepared as follows. A mixture of 50 parts of ammonium chloride and 50 parts of lactose was kneaded with a 15% ethanolic solution of 3 parts of polyvinylpyrrolidone (K-30). The resulting mixture was fed to an extrusion granulator having a screen of openings 0.8 mm wide to produce granules. The granules were then dried and blended with 0.5 part of magnesium stearate and processed by a rotary tablet machine into tablets, each of 9 mm in diameter and 250 mg in weight.

10 The emulsion-type coating liquid for the first step coating was prepared by dispersing 30 parts of an aqueous emulsion of polyvinyl-acetate ("Polysol" S-5, product of Showa Kobunshi Co. Ltd., solids content: 50 wt. %—"Polysol" is a Trade Mark), 0.6 part of titanium dioxide, 0.2 part of tartrazine aluminium lake and 2 parts of propylene glycol in 67.6 parts of water.

15 The coating solution for the second step coating was prepared by dissolving 3 parts of the same hydroxypropylmethylcellulose as used in Example 2 in 97 parts of water.

20 Into an automatic pan coater (product of Freund Industry Co., type: FM-2) were charged 2 kg of the tablets, for coating by the two step process. Conditions for the coating operation were the same as Example 3.

25 The first and second steps lasted for 90 and 30 minutes, respectively. The weight increases of the tablets after the first step and the second step were 9.0 and 10.0 mg per tablet, respectively. The surface of the tablets after the first step coating was found mat, while that after the second step very glossy.

30 **WHAT WE CLAIM IS:—**

35 1. A method of making a coated solid dosage form in which an aqueous coating liquid,

40 having a viscosity of at least 3 centipoise at the temperature of coating and containing a film-forming polymeric substance dissolved or dispersed therein, is applied to a solid dosage form.

45 2. A method according to claim 1 in which the polymeric substance is a water-soluble cellulose ether having a viscosity in the range of 1.5 to 20 centipoise as measured in a 2% by weight aqueous solution at 20°C.

50 3. A method according to claim 1 in which the coating liquid is applied in two steps, the concentration of the polymeric substance in the coating liquid applied in the second step being lower than that in the coating liquid applied in the first step.

55 4. A method according to claim 3 in which the concentration of the polymeric substance in the coating liquid applied in the first step is in the range of 5 to 25% by weight and that in the coating liquid applied in the second step is in the range of 0.5 to 10% by weight.

60 5. A method according to claim 3 or claim 4 in which the polymeric substance in the coating liquid applied in the second step is a water-soluble cellulose ether having a viscosity in the range of 1.5 to 80 centipoise as measured in a 2% by weight aqueous solution at 20°C.

65 6. A method according to any of claims 3 to 5 in which the polymeric substance in the coating liquid applied in the first step is a water-soluble cellulose ether having a viscosity in the range of 1.5 to 20 centipoise as measured in a 2% by weight aqueous solution at 20°C.

70 7. A method according to claim 1 substantially as hereinbefore described with reference to any of the Examples.

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